REMARKS

Claim 29 has been amended without prejudice in order to place the claims in condition for allowance or better form on appeal. Claim 7 has been amended to use alternative language which is permissible. The amended claims are fully supported by the specification and do not constitute new matter.

For example, inserting the hollow needle so that both the height and depth of its outlet are located within the intradermal compartment (step (a) of claim 29) is supported throughout the specification (*e.g.*, *see* Summary of the Invention at pp. 2-3), and in particular at p. 4, *l.* 29 to p. 5, *l.* 21.

Applying pressure in an amount effective to control the rate of delivery in order to obtain the desired pharmacokinetic profile (step (b) of claim 29) is supported throughout the specification (*e.g.*, *see* Summary of Invention at pp. 2-3), and in particular at p. 5, *l.* 22 to p. 6, *l.* 30.

The resulting pharmacokinetic profile (step (c) of claim 29) is supported by the specification at p. 6, *ll.* 2-6; p. 7, *ll.* 21-23, and is shown by way of example in Figs. 3 and 4.

In response to the Examiner's request for clarification of the status of the claims, claims 17-24 were withdrawn by the previous Examiner in connection with a restriction requirement (*see* Office Action dated 4/26/02, at pp. 2-3). Claims 17-24 have not been cancelled.

After entry of this amendment, claims 2-7, 10-16, and 29, as well as the withdrawn claims 17-24 will be pending in the application.

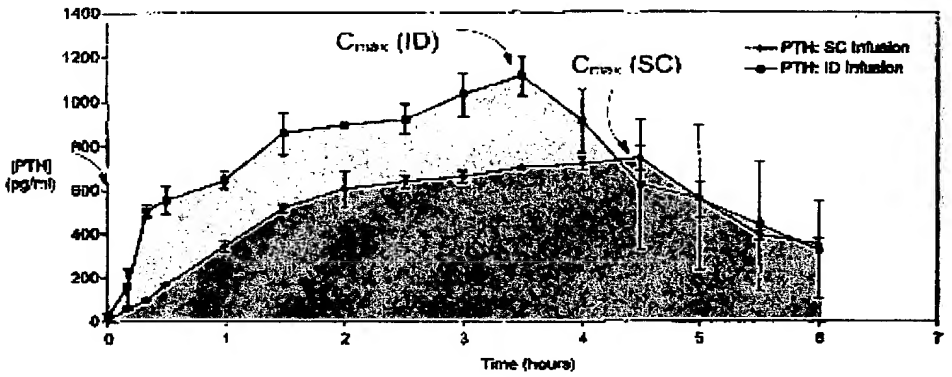
1. THE PENDING CLAIMS SATISFY THE ENABLEMENT REQUIREMENTS OF 35 U.S.C. § 112, FIRST PARAGRAPH

Claim 29 is rejected under 35 U.S.C. § 112, first paragraph, for overbreadth and lack of enablement. Specifically, the Examiner contends that the specification does not show how to achieve higher plasma concentration by intradermal injection versus subcutaneous injection for *all time periods* shown in the disclosed data (emphasis added, *see* Office Action at p. 3). This rejection is obviated by the amended claims and should be withdrawn.

At the outset, the Applicants never represented that the claimed method achieved higher plasma concentrations at *all* times tested. Quite the contrary, the specification clearly

shows that the claimed method achieves a pharmacokinetic profile similar to that exhibited by subcutaneous administration, but with a higher *maximum* plasma concentration (referred to in the art as "C_{max}") and higher bioavailability (as measured by "AUC" or area under the curve).[1] See Figs. 3 and 4 comparing the pharmacokinetic profiles achieved with the intradermal delivery method of the invention, versus subcutaneous administration (as described in the working examples at pp. 6-8).[2]

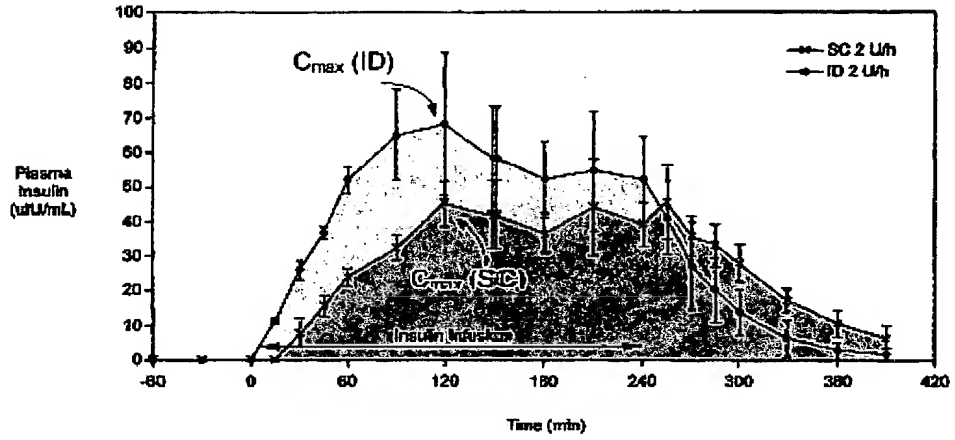
Figure 3. Plasma PTH levels.



[1] This terminology, used by skilled artisans to characterize pharmacokinetic profiles, was discussed and explained in our Amendment, filed on July 10, 2003 at p. 7.

[2] As shown by the working examples (and reflected in the figures), the maximum plasma concentration ("C_{max}") achieved using the intradermal ("ID") delivery method of the claimed invention is higher than that for subcutaneous administration ("SC"). (In Fig. 3, the C_{max} for ID delivery is 1,100 pg/mL, whereas the C_{max} for SC administration is 750 pg/mL; in Fig. 4, the C_{max} for ID delivery is 70 μIU/ml whereas the C_{max} for SC administration is 50 μIU/mL). In addition, the area under the curve ("AUC") -- the standard measure for bioavailability -- is much greater for the pharmacokinetic profile exhibited by intradermal delivery in each of Figures 3 and 4. For example, AUCs for Fig. 3 were calculated using the trapezoidal rule, commonly used by those skilled in the art, and applied to the SC and ID profiles. Graphs were first base line corrected by subtracting the respective PTH concentration at time 0 from each data point profile. The AUC value for the ID profile relative to the SC profile is 1.4 for all the times point in the profile. The AUC value resulting from ID delivery reflects a 40% increase in bioavailability relative to SC delivery.

Figure 4. Plasma Insulin levels.



The amended claims more clearly reflect these distinguishing features of the pharmacokinetic profile that are described and demonstrated by way of working examples in the specification. Thus, the amended claims are enabled, and the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

2. THE PENDING CLAIMS SATISFY THE REQUIREMENTS OF 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 2-7, 10-16, and 29 are rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential steps. This rejection is obviated in view of the amendments made herein.

The amended claims recite the steps and parameters required for practicing the method of the invention. The pending claims specify: (a) inserting the hollow needle so that its outlet (both the height and depth) is physically located within the intradermal compartment of the subject's skin, and (b) applying pressure in an amount effective to control the rate of delivery through the needle, in order to achieve (c) the recited pharmacokinetic profile.

The amended claims now recite the structural features (*e.g.*, the location of the needle outlet, the delivery of the substance into the intradermal compartment, and the identifying characteristics of the pharmacokinetic profile), as well as the functional parameters (*e.g.*, the

application of an effective amount of pressure) that satisfy the requirements of 35 U.S.C. § 112, second paragraph. *See In re Halleck,* 164 U.S.P.Q. 647, 649 (CCPA,1970) (holding "an effective amount of [compound X] for [performing a desired function] was proper), see *also*, M.P.E.P. § 2173.05(c)(III); *In re Chandler*, 138 U.S.P.Q. 243 (CCPA, 1963) ("'effective amount' admirably states what is to be derived from the disclosure of the specification as to amount").

In view of the foregoing, the rejection of claims 2-7, 10-16, and 29 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

3. THE CLAIMS ARE NOT ANTICIPATED BY THE CITED ART

The claims are rejected under 35 U.S.C. § 102(b) on the following grounds: Claims 2, 3, 5-7, 10-13 and 16 are rejected as anticipated by Gross (U.S. Patent No. 5,848,991; "Gross");[3] Claims 29, 4, 14 and 15 are rejected as anticipated by Ganderton (U.S. Patent No. 3,814,097; "Ganderton"); and Claims 29, 2, 3, 5 and 6 are rejected as anticipated by Autret (Autret *et al.*, 1991 *Therapie*, 46: 5-8; "Autret"). Each of these rejections should be withdrawn for reasons detailed below.

None of the cited references anticipates the claimed invention, because the pharmacokinetic profile specified by the claims is not disclosed, explicitly or inherently, in any of the cited references.

Of the three references cited by the Examiner, the only one that discloses a pharmacokinetic profile is Autret. However, the profile disclosed by Autret is *not* the one claimed by the Applicants. In particular, the pharmacokinetic profile disclosed by Autret (*see* Autret, Fig. 1) is virtually identical to the profile for subcutaneous delivery, and does *not* exhibit *both* a higher maximum plasma concentration *and* higher bioavailability, as is required by the currently pending claims. Autret's characterization of its own data supports the Applicant's position. See Autret at p. 5, Summary, "[*n*]*either* mean plasmatic levels at each plasmatic dosage *nor* mean *areas under the curve* ... [*i.e.*, the standard measure of bioavailability]... were significantly different" when Autret's method was compared to the subcutaneous route of administration. (emphasis supplied). As summarized by Autret, "[i]n

[3] Although claim 29 was not included in this rejection, it is the independent claim from which the rejected claims depend. Since Gross does not anticipate claim 29, or any of its dependent claims, this rejection should be withdrawn.

this study ... [Autret's method and subcutaneous routes of administration] ... are not different with regard to plasma levels ...".[4] Thus, Autret does not anticipate the claims.

The two remaining references, Gross and Ganderton, are silent as to pharmacokinetic profiles, and therefore, cannot expressly anticipate the claims. Moreover, Gross and Ganderton do not inherently achieve the pharmacokinetic profile specified in the amended claims. Each reference omits an element of the claimed method that is required to achieve the pharmacokinetic profile specified. The omission of a claimed element precludes finding anticipation under any theory -- inherency or otherwise.

Gross does not describe the insertion of a needle so that both its outlet depth and exposed height of the outlet are located within the intradermal compartment of the subject's skin.[5] This is an element of the amended claims. Without an express teaching of this element, the skilled artisan practicing Gross would not inevitably achieve the claimed invention. If the needle outlet (height and depth) is not located within the space specified in the claims, the application of pressure will not result in the pharmacokinetic profile claimed -- placement of the outlet height outside (*e.g.*, above) the intradermal compartment would result in leakage of the injected substance up and out of the injection site; placement of the outlet depth outside (*e.g.* below) the intradermal compartment would result in delivery to the subcutaneous region.[6] Thus, Gross does not anticipate the invention as claimed.

---

[4] Autret's pharmacokinetic profile supports Applicant's position that Autret never achieved true intradermal delivery -- *i.e.* a method which requires placement of the needle outlet within the intradermal compartment as specified by the amended claims. Misplacement of the needle outlet was inevitable using the mesotherapy approach described in Autret. This method involved five simultaneous injections using a 4 mm long needle at an angle of approximately 60°, and depended heavily on the skill of the practitioner. The pharmacokinetic profile reported by Autret is virtually identical to a subcutaneous injection; leading to the conclusion that Autret's mesotherapy technique resulted in subcutaneous delivery.

[5] There is no disclosure in Gross concerning height and depth of the needle outlet, or the criticality of its placement within the intradermal compartment. The Examiner erroneously contends that Gross provides needles with an outlet depth of 250 μm to 2mm (Office Action at page 4, citing Gross; col. 4, *ll.* 10-35). However a careful reading of the cited sections and the reference as a whole indicates that there is simply no disclosure in Gross relating to the relative needle length, outlet depth (or for that matter, the exposed height) of the needle. It appears, perhaps unwittingly, the Examiner has attributed teaching from the Applicant's specification into the prior art. This is improper.

[6] This is the likely explanation for the results Gross reported in his working example which show that intradermal delivery was not achieved. These were discussed previously. See Amendment dated July 14, 2003 at p. 10, n.6.

Ganderton does not describe an intradermal delivery system. Instead, Ganderton discloses a permeable pad studded with spikes (solid or hollow) used for topical application. The pad is applied to the skin so that the spikes disrupt the top layer (the stratum corneum). Drug applied on top of the permeable pad (with or without the application of pressure) diffuses through the permeable pad onto the disrupted skin. Disruption of the stratum corneum enhances absorption of the drug through the epidermis. The pad is made from permeable materials, or is made permeable using hollow needles, *and* by piercing holes through the pad in 5-10 places (Ganderton, col. 4. *ll.* 1-7). The spikes may be no more than 1000 μm in length, and do not penetrate the intradermal compartment. In Ganderton, "the penetration of the short spikes of the present device into skin is *much less* than the length of the spikes themselves" (emphasis supplied) (*See* Amendment, filed November 30, 1973 at. p. 7 in the prosecution history of Ganderton). Therefore, even if spikes of 1000 μm in length (as suggested by the Examiner) were to be used, they would never penetrate the intradermal compartment, as the penetration depth is much shallower than the spike length. Furthermore, even if Ganderton's spikes were hollow needles made at the maximum length specified by Ganderton (*i.e.* 1000 μm), the application of pressure would not result in delivering the drug through the lumen of the needles into the intradermal compartment so that the claimed pharmacokinetic profile is achieved. Instead, the drug would diffuse through the permeable pad (including the holes pierced through the pad) resulting in topical application and diffusion through the epidermis. Thus, Ganderton could not achieve the claimed pharmacokinetic profile and does not anticipate the claimed method.

In view of the foregoing, none of the cited references anticipate the amended claims, and all rejections under 35 U.S.C. § 102(b) should be withdrawn.

CONCLUSION

The Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

by: Jacqueline Benn
Reg No 43,492

Date: October 15, 2004

Laura A. Coruzzi 30,742
Laura A. Coruzzi (Reg. No.)

JONES DAY
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939